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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/676,154	09/29/2003	John Landers	M0656.70098US00	7775

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EXAMINER	
SALMON, KATHERINE D	

ART UNIT	PAPER NUMBER
1634	

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10/14/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/676,154	LANDERS ET AL.	
	Examiner	Art Unit	
	KATHERINE SALMON	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 May 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *149-160,165 and 166* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *149,150,153-160,165 and 166* is/are rejected.

7)☒ Claim(s) *151 and 152* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/23/2010*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's request for reconsideration of the finality of the rejection of the last Office action in the prebrief conference request (5/06/2010) is persuasive and, therefore, the finality of that action is withdrawn.

2. The following rejections for claims 149-160 and 165-166 are newly applied.

3. This action is NONFINAL.

Withdrawn Rejections

4. In particular based upon the Pre Brief Conference Request filed 5/06/2010 the arguments towards the teaching that neither Lisitsyn or Nikiforov teaches oligonucleotides which contain at least 50% of the polymorphic loci and less than 20% of the whole genome (p. 2 last paragraph and p. 3 2nd paragraph) has been fully reviewed and found persuasive. As such the 35 USC 103(a) rejection as obvious over Lisitsyn et al in view of Nikiforov et al. (section 10), Lisitsyn et al. And Nikiforov et al. in view of Cheung et al. (section 11), and Cheung et al. In view of Nikiforov et al. (section 12) have been withdrawn. However, it is noted that the limitations of "at least 50% in a RCG" and "less than 20% of genomic material" is suggested by the art at the time of filing as discussed below. Further, the arguments towards Lisitsyn et al and Cheung et al methods not specifically examining SNPs (p. 5 2nd -3rd paragraph) have been reviewed and found partially persuasive. It is acknowledged that Lisitsyn et al. and Cheung et al. do not specifically teach detection of SNPs, however, as discussed below the art (Shuber et al) provides a methodology to detect SNP region using RCGs.

Claim Objections

5. Claims 151-152 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

7. Claims 149, 153, 155-156, and 165-166 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shuber et al. (US Patent 5589330 December 31, 1996) in view

of Cheung et al. (Proceedings National Academy Science 1996 Vol 93 p. 14676) and Saiki et al. (WO 89/11548 November 30, 1989) .

It is noted that Cheung et al. and Saiki et al. have been previously cited on an IDS and are found in the prosecution history.

With regard to Claim 149, Shuber et al. teaches a method of detection of genetic alterations in DNA samples (Abstract). Shuber et al. teaches a method in which single base differences can be resolved (e.g. SNP) (column 5 lines 24-25). Shuber et al. teaches a method of detecting the presence or absence of the allele (a SNP) (Column 11 lines 25-30).

Shuber et al. teaches a method in which human genomic DNA is fragmented by PCR amplification (column 2 lines 26-30 and column 4 lines 10-20). The instant specification defines RCG as "a reproducible fraction of an isolated genome which is composed of a plurality of DNA fragments" (p. 15 lines 23-25 of instant specification). Further the instant specification describes RCGs as produced by PCR (p. 15 lines 30-31). Therefore a PCR derived fragment of DNA as taught by Shuber et al. would be encompassed by the definition provided. Therefore Shuber et al. teaches RCG that is PCR derived but does not teach that it is randomly prepared.

Shuber et al. teaches that ASO probes (e.g. allele specific oligonucleotides) are hybridized to RCGs (Figure 4 and column 6 lines 5-10). Shuber et al. teaches that the RCGs are immobilized to the solid support and the ASO probes are labeled. As such Shuber et al. teaches contacting a PCR derived RCG with SNP-ASOs. However,

Shuber does not teach that the ASO probes are immobilized to the surface, but rather the RCGs are immobilized.

Shuber et al. teaches a method of determining rather the RCG is complementary to different mutant alleles comprised in the ASO probe by hybridization (column 6 lines 5-10 and figure 2A). Therefore Shuber teaches a method of hybridizing the RCG to the ASO to detect allelic differences.

Shuber et al. teaches that a plurality of RCGs from different patient samples can be compared and screened for particular mutations (Figure 4 and column 7 lines 50-60). The RCG in Shuber et al. is reproducible as the RCG is produced using a PCR methodology. As such depending on which RCG preparations are compared, these RCGs would have at least 50% of the same SNP-ASP sequences. Specifically if the RCG preparations are prepared so that the same genome is reproduced than the two RCG preparations would be identical and as such include at least 50% of the same SNP-ASO sequences (e.g. 100% of the same SNP-ASO sequences).

The specification states if “a reproducible fraction is produced twice or more using the same experimental conditions the fractions produced in each repetition include at least 50% of the same sequences....For instance, if a RCG is produced by PCR another RCG can be generated under identical experimental conditions having at a minimum greater than 90% of the sequences in the first RCG". Shuber uses PCR technology to produce the RCG. As such under identical experimental conditions the amplicons made by the combination of art would be capable of producing a reproducible fraction of the genome and capable of being prepared to include at least 50% of the

same SNP-ASO sequences if two or more RCG preparations are compared to one another.

In summary, Shuber et al. teaches preparing a PCR derived reduced complexity genome using at least one PCR primer, contacting the RCG with SNP-ASOs, wherein polymorphic loci corresponding to the SNP-ASOs are present with a frequency of at least 50% in a RCG and determining the presence or absence of the SNP allele. However, Shuber does not teaches that the RCG is randomly primed; that the RCG contains less than 20% of genomic material present in a whole genome, and that the SNP-ASOs are immobilized (rather in the case of Shuber the RCG is immobilized).

With regard to Claims 155-156, Shuber et al. teaches that the length of individual ASOs may be 16 to 25 nucleotides (column 4 lines 48-49).

With regard to Claims 165 and 166, the method steps of these claims are similar to the method steps discussed above with regard to Shuber et al. Herein in the instant case, claim 165 is drawn to determining based upon the hybridization pattern the presence or absence of a SNP allele and Claim 166 is draw to determining a genotype based upon the hybridization pattern. In each of these cases, the analysis involved to determining rather the SNP-ASO is hybridized to the target RCG or is not hybridized to the target. Shuber et al. teaches such a method. Shuber et al. teaches that these ASOs can be identified such that the presence or absence of a SNP can be determined (column 5 lines 45-50). As the method of Shuber et al. teaches that one can determine the presence or the SNP by hybridization, the ordinary artisan would be able to determine the genotype of that position (e.g. the presence of the SNP).

With regard to Claims 149,165, and 166 the art at the time of filing teaches production of RCGs which are randomly primed and contain less than 20% of genomic material present in the whole genome. Cheung et al. teaches using DOP-PCR amplification to produce genomic fragments (p. 14676 2nd column DOP amplification). Cheung et al. teaches that the PCR reaction uses a DOP primer, which is degenerative (p. 14676 2nd column DOP amplification). Cheung et al. teaches that arbitrary portions of the DNA sequences are amplified by this method (p. 14676 2nd column 1st paragraph). As such Cheung et al. teaches producing randomly primer PCR derived RCGs.

Cheung et al. characterizes the DOP-PCR method as whole genome amplification, however, the methodology of Cheung et al. actually teaches that only portions of the genome is amplified and therefore less the whole genome is amplified. Cheung et al. teaches that 200 to 1000 bp fragments were produced (p. 14677 1st column 2nd paragraph). Cheung et al. teaches that only 1 of every 10 200-1000 bp pairs stretches of the human genome is amplified (p. 14678 2nd column last paragraph). Cheung et al. teaches that the human genome is about 3×10^9 bp. Therefore Cheung et al. teaches amplification of less than the whole genome. Further Cheung et al. teaches that the fractions are amplified and a plurality of fragments are produced(p. 14676 2nd column 1st paragraph), therefore Cheung et al. teaches RCG fragments as defined by the instant specification because Cheung et al. teaches amplification of less than the entire genome.

Cheung et al suggest that DOP-PCR amplified samples (e.g. the randomly-primed PCR derived RCG fragments) may be successfully used in genetic analyses such as sequencing and single stranded conformation polymorphism. However, Cheung et al. does not teach method steps of using such RCG fragments to detect SNPs or to genotype.

Specifically, Cheung et al. teaches using a DOP primer with a 6 nucleotide tag on the 3' end (p. 14676 last full paragraph). The instant specification discloses that the complexity of the resultant product when using 6 nucleotide tag on the 3' end is extremely high due to the short length, whereas the complexity of the genome is significantly reduced using 7 or 8 nucleotides on the 3' end (p. 73 liens 17-24). Cheung et al. teaches that 200 to 1000 bp fragments were produced (p. 14677 1st column 2nd paragraph). Cheung et al. teaches that only 1 of every 10 200-1000 bp pairs stretches of the human genome is amplified (p. 14678 2nd column last paragraph). Cheung et al. teaches that the human genome is about 3 X 10^9 bp. Therefore one would expect the complexity of the Cheung et al. genome of about 20% in the samples in which 200 bp fragments are produced and higher complexity as the bp fragments get larger. Therefore Cheung et al. teaches that at least about 10% is amplified and as much as 20% is amplified. As such the reduced complexity of Cheung et al. would be less than 20% of genomic material.

In summary Cheung et al. teaches preparing a randomly primer RCG which contains less than 20% of genomic material present.

With regard to Claim 153, Cheung et al. teaches using DOP-PCR amplification to produce genomic fragments (p. 14676 2nd column DOP amplification). Cheung et al. teaches that the PCR reaction uses a DOP primer, which is degenerative (p. 14676 2nd column DOP amplification). Cheung et al. teaches that arbitrary portions of the DNA sequences are amplified by this method (p. 14676 2nd column 1st paragraph).

With regard to Claims 149, 165, and 166, Saiki et al. teaches a nucleic acid hybridization assay in which oligonucleotide probes (ASO probes) are attached to a solid support matrix (abstract). Saiki et al. teaches that preparation of immobilized probes can separate in time their use, allowing for the support to be used to rapidly detecting target nucleic acid sequences in test samples on demand (p. 9 lines 24-28).

The ordinary artisan would be motivated to modify the step of making the RCG taught by Shuber et al., because Cheung et al. suggest that the ordinary artisan would be motivated to try using the DOP-PCR amplified samples (e.g. the randomly primer PCR derived RCG fragments) in other PCR based genetic analyses such as sequencing and single strand conformation polymorphism (p. 14678 2nd column 1st paragraph). As such the method of Cheung et al. would suggest a fractionalization of the genome to be used for determination of polymorphism status. Therefore the ordinary artisan would use of a DOP- PCR as taught by Chueng et al. to produce fractionalization of the genome to be used in the high throughput genomic mapping of the method of Shuber et al. to screen for specific ASO alleles in reduced complexity genomes of the whole population to screen for specific alleles which may be found anywhere in a given genome.

The ordinary artisan would have been motivated to modify the method of Shuber et al. to immobilize the ASO oligonucleotides to the solid support instead of the taught method of immobilizing the RCG to the solid support in order to prepare arrays separately and be able to test different samples quickly on premade arrays of probes. Saiki et al. teaches that preparation of immobilized probes can separate in time their sue, allowing for the support to be sued to rapidly detect target nucleic acid sequences in test samples on demand (p. 9 lines 24-28). As such the ordinary artisan would be motivated to prepare the solid supports ahead of time using the immobilization of the probe in order to produce a solid support which can be used on demand to rapidly detect SNPs in a target sequence.

8. Claims 157 and 159 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shuber et al. (US Patent 5589330 December 31, 1996), Cheung et al. (Proceedings National Academy Science 1996 Vol 93 p. 14676) and Saiki et al. (WO 89/11548 November 30, 1989) as applied to claims 149, 153, 155-156, and 165-166 and in view of Ehsani et al. (Genomics 1993 Vol. 15 p. 426).

It is noted that Ehsani has been previously cited on an IDS and is found in the prosecution history.

The method of Shuber et al, Cheung et al. and Saiki et al. teaches an RCG produced by DOP PCR used in an ASO method to detect the presence or absence of SNPs. However Shuber et al, Cheung et al, Manos et al, and Saiki et al. do not teach a method wherein the sample is tumor cells and is used to detect LOH.

Ehsani et al. teaches a method of detecting variation in breast tumors by ASO hybridization techniques (abstract). With regard to Claim 157, Ehsani et al teaches that ASO techniques allows for the determination of loss of heterozygosity (p. 428 lat paragraph).

With regard to Claim 153, Cheung et al. teaches using DOP-PCR amplification to produce genomic fragments (p. 14676 2nd column DOP amplification).

Therefore it would be prima facie obvious to one of ordinary skill in the art at the time of filing to modify the method of Shuber et al., Cheung et al., and Saiki et al to use tissue selected for loss of heterozygosity such as tumor cells as taught by Ehsani et al. The ordinary artisan would be motivated to use the method of Shuber et al, Cheung et al. and Saiki et al. to detect tumor samples because Ehsani et al. teaches that ASO detection can identity polymorphic markers that contribute to disease such as cancer (p. 426 1st paragraph). It would have been obvious to one of ordinary skill in the art at the time the invention was made to use tumor samples in the method of detecting SNPs of Shuber et al., Cheung et al., and Saiki et al. with a reasonable expectation of success because the prior art of Ehsani suggests that these samples may be successfully used in ASO assays for the detection of polymorphic markers for the detection of LOH.

9. Claims 149-150, 154-156 and 165-166 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shuber et al. (US Patent 5589330 December 31, 1996) in view of Lisitsyn et al. (Science Feb 1993 Vol. 259 p. 948) and Saiki et al. (WO 89/11548 November 30, 1989).

It is noted that Lisitsyn et al. has previously been cited on an IDS and the art may be found within the prosecution history.

With regard to Claim 149, Shuber et al. teaches a method of detection of genetic alterations in DNA samples (Abstract). Shuber et al. teaches a method in which single base differences can be resolved (e.g. SNP) (column 5 lines 24-25). Shuber et al. teaches a method of detecting the presence or absence of the allele (a SNP) (Column 11 lines 25-30).

Shuber et al. teaches a method in which human genomic DNA is fragmented by PCR amplification (column 2 lines 26-30 and column 4 lines 10-20). The instant specification defines RCG as "a reproducible fraction of an isolated genome which is composed of a plurality of DNA fragments" (p. 15 lines 23-25 of instant specification). Further the instant specification describes RCGs as produced by PCR (p. 15 lines 30-31). Therefore a PCR derived fragment of DNA as taught by Shuber et al. would be encompassed by the definition provided. Therefore Shuber et al. teaches RCG that is PCR derived but does not teach that it is randomly prepared.

Shuber et al. teaches that ASO probes (e.g. allele specific oligonucleotides) are hybridized to RCGs (Figure 4 and column 6 lines 5-10). Shuber et al. teaches that the RCGs are immobilized to the solid support and the ASO probes are labeled. As such Shuber et al. teaches contacting a PCR derived RCG with SNP-ASOs. However, Shuber does not teach that the ASO probes are immobilized to the surface, but rather the RCGs are immobilized.

Shuber et al. teaches a method of determining rather the RCG is complementary to different mutant alleles comprised in the ASO probe by hybridization (column 6 lines 5-10 and figure 2A). Therefore Shuber teaches a method of hybridizing the RCG to the ASO to detect allelic differences.

Shuber et al. teaches that a plurality of RCGs from different patient samples can be compared and screened for particular mutations (Figure 4 and column 7 lines 50-60). The RCG in Shuber et al. is reproducible as the RCG is produced using a PCR methodology. As such depending on which RCG preparations are compared, these RCGs would have at least 50% of the same SNP-ASP sequences. Specifically if the RCG preparations are prepared so that the same genome is reproduced than the two RCG preparations would be identical and as such include at least 50% of the same SNP-ASO sequences (e.g. 100% of the same SNP-ASO sequences).

The specification states if “a reproducible fraction is produced twice or more using the same experimental conditions the fractions produced in each repetition include at least 50% of the same sequences....For instance, if a RCG is produced by PCR another RCG can be generated under identical experimental conditions having at a minimum greater than 90% of the sequences in the first RCG". Shuber uses PCR technology to produce the RCG. As such under identical experimental conditions the amplicons made by the combination of art would be capable of producing a reproducible fraction of the genome and capable of being prepared to include at least 50% of the same SNP-ASO sequences if two or more RCG preparations are compared to one another.

In summary, Shuber et al. teaches preparing a PCR derived reduced complexity genome using at least one PCR primer, contacting the RCG with SNP-ASOs, wherein polymorphic loci corresponding to the SNP-ASOs are present with a frequency of at least 50% in a RCG and determining the presence or absence of the SNP allele. However, Shuber does not teaches that the RCG is randomly primed; that the RCG contains less than 20% of genomic material present in a whole genome, and that the SNP-ASOs are immobilized (rather in the case of Shuber the RCG is immobilized).

With regard to Claims 155-156, Shuber et al. teaches that the length of individual ASOs may be 16 to 25 nucleotides (column 4 lines 48-49).

With regard to Claims 165 and 166, the method steps of these claims are similar to the method steps discussed above with regard to Shuber et al. Herein in the instant case, claim 165 is drawn to determining based upon the hybridization pattern the presence or absence of a SNP allele and Claim 166 is draw to determining a genotype based upon the hybridization pattern. In each of these cases, the analysis involved to determining rather the SNP-ASO is hybridized to the target RCG or is not hybridized to the target. Shuber et al. teaches such a method. Shuber et al. teaches that these ASOs can be identified such that the presence or absence of a SNP can be determined (column 5 lines 45-50). As the method of Shuber et al. teaches that one can determine the presence or the SNP by hybridization, the ordinary artisan would be able to determine the genotype of that position (e.g. the presence of the SNP).

With regard to Claims 149,165, and 166 the art at the time of filing teaches production of RCGs which are randomly primed and contain less than 20% of genomic material present in the whole genome

With regard to Claims 149, 165, 166, Lisitsyn et al. teaches a method of producing reduced complexity genomes (p. 946 3rd column 1st paragraph). Lisitsyn et al. teaches a method of producing these reduced complexity genomes using adapter linked PCR wherein the RCG is prepared by restriction enzyme cleavage of the genomic DNA followed by ligation of at least one adapter sequence (p. 946 3rd column 2nd paragraph).

Lisitsyn et al. teaches a method of reducing the complexity of the resulting amplicons to be 55 times, 13 times and 8 times less than the starting genomic DNA (p. 946 3rd column 2nd paragraph). Lisitsyn et al. teaches that when a six base pair cutter (i.e. Bam HI, BgI II, or Hind III) is used to cut genomic DNA followed by amplification at least 10000 fragments will be obtained which are below 1 kb (p. 946 3rd column 1st and 2nd paragraph). Therefore Lisitsyn teaches enriched subsets that are approximately 1/16 (when BgI II is used) and approximately 1/64 (wherein Bam HI was used) the complexity of the unenriched sample. As such these subsets represent less than less than 5% of the starting material. Lisitsyn suggests a method of producing RCG representing less than 5% of the genome.

Lisitsyn et al. teaches that using this type of PCR fractionalizing of the whole genome can be made (column 946 3rd column 2nd paragraph). As such the method of Lisitsyn et al. would suggest a fractionalization of the genome to be used for genome

wide scanning. Shuber et al. teaches a method of high throughput screening (abstract). Therefore it would be obvious that the method of Shuber could be used for genome wide scanning.

With regard to Claim 150, as discussed above, Lisitsyn suggests a method of producing RCG representing less than 5% of the genome.

With regard to Claim 154, Lisitsyn et al. teaches a method of producing these reduced complexity genomes using adapter linked PCR wherein the RCG is prepared by restriction enzyme cleavage of the genomic DNA followed by ligation of at least one adapter sequence (p. 946 3rd column 2nd paragraph).

With regard to Claim 149, Saiki et al. teaches a nucleic acid hybridization assay in which oligonucleotide probes (ASO probes) are attached to a solid support matrix (abstract). Saiki et al. teaches that preparation of immobilized probes can separate in time their use, allowing for the support to be sued to rapidly detecting target nucleic acid sequences in test samples on demand (p. 9 lines 24-28).

Therefore it would be prima facie obvious at the time of filing to modify the method of Shuber et al. to replace the method steps of PCR with the method steps of adapter linker PCR as taught by Lisitsyn et al. and to immobilize the ASO oligonucleotides to the solid support as taught by Saiki et al.

The ordinary artisan would be motivated to modify the step of making the RCG taught by Shuber et al., because Lisitsyn et al. teaches that the RCGs produced by the method of adapter linker PCR can be used to find small differences between the sequences of two DNA populations (p. 946 1st column 1st paragraph). Lisitsyn et al.

teaches that using this type of PCR fractionation can be made in which the whole genome reduced complexity is represented (column 946 3rd column 2nd paragraph). As such the method of Lisitsyn et al. would suggest a fractionalization of the genome to be used for genome wide scanning. Therefore the ordinary artisan would use of an adapter linker PCR as taught by Listen to produce fractionalization of the genome to be used in the high throughput genomic mapping of the method of Shuber et al. to screen for specific ASO alleles in reduced complexity genomes of the whole population to screen for specific alleles which may be found anywhere in a given genome.

The ordinary artisan would have been motivated to modify the method of Shuber et al. to immobilize the ASO oligonucleotides to the solid support instead of the taught method of immobilizing the RCG to the solid support in order to prepare arrays separately and be able to test different samples quickly on premade arrays of probes. Saiki et al. teaches that preparation of immobilized probes can separate in time their sue, allowing for the support to be sued to rapidly detect target nucleic acid sequences in test samples on demand (p. 9 lines 24-28). As such the ordinary artisan would be motivated to prepare the solid supports ahead of time using the immobilization of the probe in order to produce a solid support which can be used on demand to rapidly detect SNPs in a target sequence.

10. Claims 157-158 and 160 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shuber et al. (US Patent 5589330 December 31, 1996), Lisitsyn et al. (Science Feb 1993 Vol. 259 p. 948), and Saiki et al. (WO 89/11548 November 30,

1989) as applied to Claims 149-150, 154-156 and 165-166 and in view of Ehsani et al. (Genomics 1993 Vol. 15 p. 426).

The method of Shuber et al, Lisitsyn et al, and Saiki et al. teaches an RCG produced by adapter linker PCR used in an ASO method to detect the presence or absence of SNPs. However Shuber et al, Lisitsyn et al, Saiki et al. do not teach a method wherein the sample is tumor cells and is used to detect LOH.

Ehsani et al. teaches a method of detecting variation in breast tumors by ASO hybridization techniques (abstract). With regard to Claim 157, Ehsani et al teaches that ASO techniques allows for the determination of loss of heterozygosity (p. 428 lat paragraph).

With regard to Claim 158, Lisitsyn et al. teaches a method of reducing the complexity of the resulting amplicons to be 55 times, 13 times and 8 times less than the starting genomic DNA (p. 946 3rd column 2nd paragraph). Lisitsyn et al. teaches that when a six base pair cutter (i.e. Bam HI, Bgl II, or Hind III) is used to cut genomic DNA followed by amplification at least 10000 fragments will be obtained which are below 1 kb (p. 946 3rd column 1st and 2nd paragraph). Therefore Lisitsyn teaches enriched subsets that are approximately 1/16 (when Bgl II is used) and approximately 1/64 (wherein Bam HI was used) the complexity of the unenriched sample. As such these subsets represent less than less than 5% of the starting material. Lisitsyn suggests a method of producing RCG representing less than 5% of the genome.

With regard to Claim 160, Lisitsyn et al. teaches a method of producing these reduced complexity genomes using adapter linked PCR wherein the RCG is prepared

by restriction enzyme cleavage of the genomic DNA followed by ligation of at least one adapter sequence (p. 946 3rd column 2nd paragraph).

Therefore it would be prima facie obvious to one of ordinary skill in the art at the time of filing to modify the method of Shuber et al., Lisitsyn et al., Saiki et al to use tissue selected for loss of heterozygosity such as tumor cells as taught by Ehsani et al. The ordinary artisan would be motivated to use the method of Shuber et al, Lisitsyn et al, and Saiki et al. to detect tumor samples because Ehsani et al. teaches that ASO detection can identity polymorphic markers that contribute to disease such as cancer (p. 426 1st paragraph). It would have been obvious to one of ordinary skill in the art at the time the invention was made to use tumor samples in the method of detecting SNPs of Shuber et al., Lisitsyn et al, and Saiki et al. with a reasonable expectation of success because the prior art of Ehsani suggests that these samples may be successfully used in ASO assays for the detection of polymorphic markers.

Conclusion

11. No claims are allowed.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to KATHERINE SALMON whose telephone number is (571)272-3316. The examiner can normally be reached on Monday - Friday 9AM-530PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached on (571) 272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Katherine Salmon

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